II. REMARKS/ARGUMENTS

A. Regarding the Amendments

In the specification, the first paragraph at page 9 has been amended to include additional deposit information as suggested by the Examiner.

Claims 5-8, 11-14, and 18-53 remain in this application. Claims 1-4, 9-10, and 15-17 have been cancelled. Claims 5-8, 11-14, and 18-24 have been withdrawn as the result of an earlier restriction requirement. In view of the Examiner's earlier restriction requirement, applicant retains the right to present claims 5-8, 11-14, and 18-24 or equivalents thereof in a divisional or later filed application.

Claims 25, 28-29, 31, 40, 43-44, and 46 have been amended based on Examiner's suggestions. In addition, claims 25 and 40 have been amended to recite that the chimeric antibody elicits a humoral immune response "in the oral cavity of the subject" and "the portion of the monoclonal antibody that triggers the humoral immune response is from the same species of the subject." Claim 25 has also been amended to recite that the chimeric antibody is administered to "the oral cavity of a subject". Support can be found, *inter alia,* at page 3, lines 20-26, page 4, lines 1-2, page 5, lines 10-18, page 11, lines 23-27, and page 12, lines 1-5 in the specification. No new matter is added by the amendments. Entering of the amendments is respectfully requested.

Applicants wish to draw the Examiner's attention to amendments to the drawings and specification, including the Sequence Listing, submitted on March 13, 2003. An indication of the Examiner's approval of the proposed drawing correction and entering of the amendments is respectfully requested.

B. Provisional Double Patenting

Claims 25, 35, and 37-38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 4, 7, 10, 12

and 17 of copending Application No. 09/378,577. Applicants will not comment on the merit of this provisional rejection and reserve the right to respond to this provisional rejection if any of the claims at issue in the copending Application No. 09/378,577 has been allowed.

C. Claim Objections

Claims 28 and 43 are objected to because of the informalities. Applicants respectfully submit that such objection is moot in light of the amendments made to these claims. Withdrawal of the objection is respectfully requested.

D. Rejections under 35 U.S.C. §112, first paragraph

Claims 28 and 43 are rejected under 35 U.S.C. §112, first paragraph as the deposits recited in the claims are allegedly only in partial compliance with biological deposit requirements.

Applicants submit herein, as Exhibit A, a copy of the "Statement of Deposit Conditions Under 37 C.F.R. §1.808", which was submitted in U.S. application serial No. 09/292,635, now issued as U.S. Patent No. 6,231,857, with respect to the deposits recited in the claims at issue. As indicated in the Statement, the deposits were made under the terms of the Budapest Treaty and all restrictions imposed by the depositor on the availability of the deposited material to the public will be irrevocably removed upon the granting of a patent on the application. A copy of the deposit receipt is also attached hereto as Exhibit A. In addition, the specification (first paragraph at page 9) has been amended to include additional deposit information as suggested by the Examiner.

Therefore, the deposits recited in the claims are in full compliance with the biological deposit requirements. Withdrawal of the rejection is respectfully requested.

E. Rejections under 35 U.S.C. §112, second paragraph

Claims 25-53 are rejected under 35 U.S.C. §112, second paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention.

Claim 25 has been amended to recite "an antigen of the cariogenic organism" and that the binding region is "derived from a species other than that of the treated subject" as suggested by the Examiner.

Claims 28 and 43 have been amended to delete the recitation of "SWLA2 and SWLA3" in light of the restriction requirement. Applicants reserve the right to pursue the inventions directed to SWLA2 and SWLA3 at a later stage.

Claims 29, 31, 44 and 46 have been amended to recite that the variable region "comprises the amino acid sequence as shown in SEQ ID NO....".

Claim 40 has been amended to recite that the binding region is "derived from a species other than that of the subject to be treated with said chimeric monoclonal antibody" as suggested by the Examiner.

Claims 25-53 as amended particularly point out and distinctly claim the subject matter which applicants regard as the invention. Withdrawal of the rejection is respectfully requested.

F. Rejections under 35 U.S.C. §103

Claims 25-53 have been rejected under 35 U.S.C. §103 as allegedly being obvious over cited prior art. Before responding specifically to each rejection, Applicants would like to first address these rejections in general.

It seems to be the overall believe of the Office Action that the present invention is about humanizing murine antibodies against *S. mutans* and using them generically to treat dental caries. Applicants respectfully submit that the present invention is much more than humanization of murine antibodies against *S. mutans*. It is the discovery of the present invention that instead of blocking bacteria from binding to dental surfaces, one can use certain chimeric antibodies to elicit a humoral immune response right inside the oral cavity and using such humoral immune response to kill cariogenic organisms.

Such discovery is especially significant since it was against the "odds" at the time of the present invention. Prior to the present invention, it was generally believed that oral immune-apparatus was not capable of producing humoral immune response because it lacked the necessary IgG and IgM antibodies. Therefore the main approach to treat dental caries at the time was to block the binding of bacteria to dental surfaces by causing bacteria clumping. Such

approach led to the development of methods and antibodies directed at causing bacteria aggregation. It is because of the present invention, one realizes that artificially introduced IgG or IgM antibodies are capable of working with naturally existing oral immune-apparatus to develop humoral immune response right inside the oral cavity and such humoral immune response can be used to kill cariogenic organisms. This new understanding revolutionized the approach for treating dental caries and it led to the development of methods and antibodies directed at causing humoral immune response in oral cavity instead of bacteria aggregation.

The prior art cited in the Office Action may or may not collectively disclose a humanized murine monoclonal antibody against *S. mutans*. Regardless, none of the cited prior art disclose or suggest using of humoral immune response to treat dental caries. Without the discovery and newly found appreciation provided by the present invention, one skilled in the art would not have been motivated to use the methods or antibodies provided in the present invention to treat dental caries since they would have been viewed as unconventional and against the "odds". Even if they did for the sake of the argument, they would not have had reasonable expectation for success since again using the methods and antibodies provided in the present invention to treat dental caries would have been viewed as highly unpredictable because of the general perception of the oral immune apparatus, especially its lacking of necessary antibodies in naturally providing humoral immune response.

With these discussions in mind, Applicants would like to specifically address each rejection as the following.

1. *The rejections of claims 25-35, 37-50 and 52-53 under 35 U.S.C. §103(a) as allegedly being unpatentable over Shi et al., (Hybridom Volume 17 No. 4, 1998, pages 365-371) in view of Carter et al. (WO 92/22653) is respectfully traversed.*

Applicants respectfully submit that Shi et al., disclose three murine monoclonal antibodies against *S. mutans* and their use in detecting the presence of *S. mutans* and diagnosing dental caries. Shi et al., do not disclose or enable using these new murine monoclonal antibodies in therapeutic treatment of dental caries. At the end of the article, Shi et al., states that "these new MAbs are particularly useful for diagnostic purposes and they may have great impact on future basic and clinical studies and the diagnosis and treatment on human dental caries." The Office Action relies on this single statement in the entire article as motivating one skilled in the

art to humanize the disclosed murine monoclonal antibodies and humanize them in a specific way so that they can be used in the present invention.

Applicants respectfully submit that the Office Action is using the statement out of context and as a hindsight. When the entire article of Shi et al., is devoted to using the three murine monoclonal antibodies in detecting *S. mutans* and when it is known that diagnosis of a condition is closely related to the treatment of the condition, it is logical to interpret the statement as stating that the new monoclonal antibodies may have great impact on the diagnosis of human dental caries and such diagnosis may have great impact on the treatment of human dental caries. Such interpretation is especially reasonable in light of the fact that this is the only statement that makes any reference to the treatment of dental caries and such statement is within the same sentence emphasizing the use of the monoclonal antibodies for diagnostic purposes. Furthermore, except this single statement Shi et al., do not discuss whether these murine antibodies could be used and how they could be used in treating dental caries. Therefore the interpretation relied upon by the Office Action is unsupported and self-serving.

Carter is cited as a secondary reference. Carter et al., disclose the general method of making humanized antibodies and the use thereof.

None of the cited prior art disclose or suggest using humanized antibodies capable of eliciting a humoral immune response in the oral cavity to treat human dental caries. As explained under the general discussion provided above, without the benefit of understanding the discovery that underlies the present invention one skilled in the art would have thought using a chimeric antibody to elicit a humoral immune response in the oral cavity was against the "odds" since the oral immune apparatus lacks the necessary antibodies, *e.g.*, IgG and IgM for humoral immune response and the oral immune apparatus does not naturally provide humoral immune response.

In addition, even if for the sake of argument that one skilled in the art would have been motivated to humanize the murine monoclonal antibodies provided in Shi et al., the general approach of blocking cariogenic organism from binding to dental surfaces would have led one skilled in the art to humanize the murine antibodies as IgA antibodies suitable for clumping bacteria, but not as IgG or IgM antibodies suitable for triggering humoral immune response.

In summary, Shi et al., and Carter et al., alone or in combination fail to teach or suggest using chimeric antibodies that are capable of inducing humoral immune response in the oral cavity to treat dental caries. Therefore, the claims at issue are not obvious over the cited prior art. Withdrawal of the rejection is respectfully requested.

2. The rejections of claims 25-27, 33-42, and 48-53 under 35 U.S.C. §103(a) as allegedly being unpatentable over Ma et al. (European Journal of Immunology 1994 Vol. 24(1) pages 131-138) in view of Adair et al. (U.S. Patent 5,877,293) or Carter et al. (WO 92/22653) is respectfully traversed.

Applicants respectfully submit that Ma et al., are directed primarily to expressing a murine IgG1 antibody in transgenic plants. Ma et al., do not teach or suggest the present invention. On the contrary, Ma et al., teach away from using the methods and antibodies provided by the present invention to treat dental caries.

According to Ma et al., the murine IgG1 antibody Guy's 13 prevents adherence and colonization of *S. mutans in vivo*. Ma et al., believe that the protective effect of Guy's 13 is provided by the binding of the antibody to the bacteria, and is not provided by the region responsible for triggering humoral immune response. Specifically Ma states that the protective effect of Guy's 13 is "epitope specific, as not all anti-SA I/II mAb were effective[9]" and "[t]he Fc-mediated functions of the mAb were not essential, as the F(ab')2 portion was as protective as the intact IgG,..." (See page 131, bottom of the left column, emphasis added). Ma et al., further conclude at the end of the article that " [a]lthough the maintenance of bivalent antigen binding of the antibody molecule was required for prevention of colonization of *S. mutans in vivo*, the functional Ig regions that are involved in complement binding and opsonization through cellular interactions are not essential." (See page 136, last paragraph). Therefore, Ma et al., clearly teach that the epitope binding of the Guy'13 antibody is critical to its protective function against *S. mutans* whereas Fc-mediated functions of the antibody such as eliciting a humoral immune response through complement binding or cellular interactions is dispensable since deletion of the Fc region of the Guy's 13 did not have any impact on the protective effect of Guy's 13.

Ma et al., further promote such teaching by testing the expression of not only Guy'13, but also two other IgG-IgA hybrids of Guy's 13 to see whether the constant region of IgA can enhance the protective effect of Guy's 13. The constant region of IgA does not include a complete Fc region[1], thus does not trigger Fc-mediated humoral immune response in mucosal environment. Ma et al., believe, however, that the constant region of IgA, *i.e.*, Cα2 and Cα3 which contain the J chain and secretory component binding sites increases the valency and resistance to proteolytic activity of the IgG-IgA hybrid antibody and is advantageous, especially when the bacterial aggregation is the important effector mechanism. (See the last paragraph of page 136 and the first paragraph of page 137.) Therefore, by replacing large part of the IgG constant region with the IgA constant region, Ma et al., have truncated the Fc region of IgG and followed their own teaching that the constant regions responsible for eliciting humoral immune response are not important for the treatment and prevention of dental caries. Ma's data obtained from the hybrid antibodies demonstrated that for the protective effect offered by Ma's antibody, the regions responsible for eliciting humoral immune response not only can be deleted, but also can be replaced by other constant regions that do not contain a functional Fc region for eliciting humoral immune response.

Therefore, Ma et al., conclude that the Ig regions responsible for eliciting a humoral immune response are dispensable since deletion of these regions made no impact on the protective effect of the antibody. Thus Ma et al., teach away from the present invention, *e.g.*, Ma et al., teach away from using a chimeric antibody capable of eliciting humoral immune response to treat dental caries.

Furthermore, Applicants respectfully point out that Ma et al., have disclosed the expression of three different forms of antibodies in plants: 1) IgG Guy's 13, 2) IgG-IgA Guy's 13 with one IgG and two IgA constant regions, and 3) IgG-IgA Guy's 13 with two IgG and two IgA constant regions. According to the functional assays performed by Ma et al., all three antibodies caused aggregation of *S. mutans* at similar level and none of these antibodies

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[1] The Fc region includes CH2 and CH3. The constant region of IgG includes CH1, CH2, and CH3 whereas the constant region of IgA includes CH1 and CH2.

appeared to affect *S. mutans* rate of growth (page 136, under 3.5). Therefore, without any teaching or guidance even if one skilled would have humanized Guy's 13, she or he would have used the constant region of IgA as suggested and illustrated by Ma et al., and would not have used the constant region of IgG, which was deleted and shown by Ma et al., as dispensable in treating dental caries. It is purely hindsight for the Office Action to assert that based on Ma et al., one skilled in the art would have humanized Guy's 13, and would have humanized Guy's 13 in a way not relevant to causing bacteria clumping, which was taught by Ma et al., but in a way relevant to causing humoral immune response, which not only was not suggested by Ma et al., but also was against the general perception of the oral immune apparatus.

The Office Action relies on a single statement of Ma et al., to support its position that constant region of IgG is suggested by Ma et al. Applicants respectfully submit that the statement of Ma et al., is used out of context and as hindsight by the Office Action. Specifically the Office Action cites the statement from Ma et al., as "incorporating other regions such as the complement binding region of human IgG". Applicants respectfully point out that the full statement of Ma et al., really starts by stating that "for other antibodies, there might be significant advantages in incorporating other functional regions, such as the complement-binding domain from a human IgG1 antibody or domains containing regions that act as receptors for cell- or tissue-specific molecules." (emphasis added). Therefore, "incorporating the complement-binding domain from a human IgG1 antibody" is really directed to manipulation of antibodies for plant expression in general and for other antibodies other than the antibodies illustrated in Ma et al., *e.g.*, specifically excluding the antibodies illustrated in Ma et al.

In summary, Ma et al., are focused on expressing murine antibody Guy's 13 in plants and modify Guy's 13 to enhance its ability to cause bacteria aggregation by deleting the constant region of IgG and replacing it with the constant region of IgA. Ma et al., do not teach or suggest using a chimeric antibody capable of eliciting humoral immune response in the oral cavity to treat dental caries.

Adair and Carter are cited as secondary references. Adair discloses the making of a humanized antibody against carcinoembryonic antigen. Carter discloses making humanized

antibody in general. Adair and Carter do not cure the deficiency of Ma et al., because they too fail to teach or suggest using chimeric antibodies capable of eliciting humoral immune response in the oral cavity to treat dental caries.

In conclusion, Ma, Adair, and Carter, alone or in combination fail to teach or suggest using chimeric antibodies that are capable of inducing humoral immune response in oral cavity to treat dental caries. Therefore the claims at issue are not obvious over the cited prior art. Withdrawal of the rejections is respectfully requested.

In view of the amendment and the above remarks, it is submitted that the claims are in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Respectfully Submitted,
Gray Cary Ware & Freidenrich LLP

Dated: 10/1/03

By _____
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RESPONSE UNDER
RULE 1.116 -
EXPEDITED PROCEDURE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Shi and Hume	Examiner:	J. Graser
Serial No.:	09/292,635	Group Art Unit:	1641
Filed:	August 20, 1999	Docket:	510030-196
Due Date:	November 1, 2000	Date Mailed:	October 27, 2000

Title: **NOVEL ANTIBODIES TO *S. MUTANS* AND USES THEREOF**

CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service, as first class mail, with sufficient postage, in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231, on October 27, 2000.

By: _____
Name: Gayle Vinson

STATEMENT OF DEPOSIT CONDITIONS UNDER 37 C.F.R. § 1.808

Honorable Assistant Commissioner for Patents
Washington, D.C. 20231

Dear Sir:

The undersigned hereby states that the deposit of the hybridomas HB-12558, HB-12559, and HB-12560, producing the monoclonal antibodies designated SWLA3, SWLA1, and SWLA2, respectively, was made with the American Type Culture Collection, located at 10801 University Boulevard, Manassas, Virginia 20110-2209, on August 25, 1998. The deposit was made under the terms of the Budapest Treaty. A copy of the deposit receipt is attached hereto as Exhibit A.

The undersigned hereby further states that all restrictions imposed by the

EXHIBIT A

depositor on the availability of the deposited material to the public will be irrevocably removed upon the granting of a patent on this application.

Respectfully submitted,

Dated: October 27, 2000

Michael B. Farber
Registration No. 32,612

OPPENHEIMER WOLFF & DONNELLY LLP
2029 Century Park East, 38th Floor
Los Angeles, California 90067-3024
(310) 788-5000

EXHIBIT A

ATCC

10801 University Blvd • Manassas, VA 20110-2209 • Telephone: 703-365-2700 • FAX: 703-

BUDAPEST TREATY ON THE INTERNATIONAL RECOGNITION OF
THE DEPOSIT OF MICROORGANISMS FOR THE PURPOSES OF PATENT PROCEDURE

INTERNATIONAL FORM

RECEIPT IN THE CASE OF AN ORIGINAL DEPOSIT ISSUED PURSUANT TO RULE 7.3
AND VIABILITY STATEMENT ISSUED PURSUANT TO RULE 10.2

To: (Name and Address of Depositor or Attorney)

Mandel & Adriano
Attn: Sarah B. Adriano
35 N. Arroyo Parkway, Suite 60
Pasadena, CA 91103

Deposited on Behalf of: The Regents of the University of California
(Ref. Docket 30435.61USP1)

Identification Reference by Depositor:	**ATCC Designation**
B-lymphocytes and myeloma hybridoma cell SWLA3	HB-12558
B-lymphocytes and myeloma hybridoma cell SWLA1	HB-12559
B-lymphocytes and myeloma hybridoma cell SWLA2	HB-12560

The deposits were accompanied by: ___ a scientific description _ a proposed taxonomic description indicated above. The deposits were received August 25, 1998 by this International Depository Authority and have been accepted.

AT YOUR REQUEST: X We will inform you of requests for the strains for 30 years.

The strains will be made available if a patent office signatory to the Budapest Treaty certifies one's right to receive, or if a U.S. Patent is issued citing the strains, and ATCC is instructed by the United States Patent & Trademark Office or the depositor to release said strains.

If the cultures should die or be destroyed during the effective term of the deposit, it shall be your responsibility to replace them with living cultures of the same.

The strains will be maintained for a period of at least 30 years from date of deposit, or five years after the most recent request for a sample, whichever is longer. The United States and many other countries are signatory to the Budapest Treaty.

The viability of the cultures cited above was tested September 14, 1998. On that date, the cultures were viable.

International Depository Authority: American Type Culture Collection, Manassas, VA 20110-2209 USA.

Signature of person having authority to represent ATCC:

Barbara M. Hailey, Administrator, Patent Depository

Date: September 14, 1998